# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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# PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

| | |
|---|---|
| | Date of mailing *(day/month/year)* 27 DEC 2005 |
| Applicant's or agent's file reference<br>4649-4000PC | FOR FURTHER ACTION<br>See paragraph 2 below |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US05/06930 | 03 March 2005 (03.03.2005) | 03 March 2004 (03.03.2004) |

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 38/00, 39/02 and US Cl.: 514/2, 951; 530/300, 350; 424/236.1, 278.1, 405

Applicant

ESSENTIA BIOSYSTEMS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☒ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis(b)* that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

| Name and mailing address of the ISA/ US | Authorized officer |
|---|---|
| Mail Stop PCT, Attn: ISA/US<br>Commissioner for Patents<br>P.O. Box 1450<br>Alexandria, Virginia 22313-1450<br>Facsimile No. (703) 305-3230 | Samuel W. Liu<br>Telephone No. 571-272-1600 |

Form PCT/ISA/237 (cover sheet) (January 2004)

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

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**Box No. I Basis of this opinion**

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language ____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing

      ☐ contained in international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

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**Box No. IV Lack of unity of invention**

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has:
   - ☒ paid additional fees
   - ☐ paid additional fees under protest
   - ☐ not paid additional fees
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
   - ☐ complied with
   - ☒ not complied with for the following reasons:

   See the lack of unity section of the International Search Report(Form PCT/ISA/210)

4. Consequently, this opinion has been established in respect of the following parts of the international application:
   - ☐ all parts.
   - ☒ the parts relating to claims Nos. 1-3,7-33,68-75,78-80 and 197-211

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

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**Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 20-21 | YES |
| | Claims | 1-3, 7-19, 22-33, 68-75, 78-80 and 197-211 | NO |
| Inventive step (IS) | Claims | 1-3, 7-33, 68-75, 78-80 and 197-211 | YES |
| | Claims | NONE | NO |
| Industrial applicability (IA) | Claims | 1-3, 7-33, 68-75, 78-80 and 197-211 | YES |
| | Claims | NONE | NO |

2. Citations and explanations:

Please See Continuation Sheet

**WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY**

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**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claims 8-15 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claim 8 recitation "the backbone comprises a positively charged polypeptide" is indefinite in that the polypeptide backbone is not positively charged but its side chain, e.g., lysine. Claims 9-15 which depend from claim 8 are also objected to.

**Supplemental Box**
**In case the space in any of the preceding boxes is not sufficient.**

**V. 2. Citations and Explanations:**
Claims 1-3, 7-19, 22-33, 68-75, 78-80 and 197-211 lack novelty under PCT Article 33(2) and inventive step under PCT Article 33(3) as being anticipated by and obvious over, respectively, by Waugh, J, et al. (A) (WO 03072049 A2), Robins, P. D. et al. (US 2003/01014622 A1), Hunt, T. J. (US 2003/0118598 A1), Dowdy, S. (WO 0034308), Park, J. S. et al. (US Pat. No. 6217912 B1), Chen F. et al. (US 2001/0024716 A1), Qin, J. et al. (US Pat No. 5985434), Schwartz, J. J. et al. (*Current Opin. Mol. Therapeutic.* (2000) 2(2), 162-167), Waugh, J. et al. (B) (WO 0207773 A2), Waugh J. et al. (US 2003/0229034 A1), Mahato R. I. et al. (US Pat. No. 6696038), and Apt, D. et al. (US 2004/0009469 A1).

In the patent claims 19-22, Waugh et al. (A) teach a composition comprising a biologically active polypeptide, i.e., vascular endothelial growth factor (VEGF), which does not therapeutically alter blood glucose level and a carrier which reads on the peptide formula set forth in instant claim 29; the said carrier molecule comprises a positively charged backbone having a plurality of attached efficiency groups (claim 19) wherein association between the VEGF and the carrier is non-covalent. The Waugh et al. teachings are applied to instant claims 1-3 and 22 and 28-29.

Since the VEGF has therapeutic activity, the above the Waugh et al. teachings are applied to instant claim 6.

In the patent claims 23, Waugh et al. (A) teach that the positively charged backbone molecule is a polylysine which has molecular weight between 150 KDa to 300 KDa, as applied to instant claims 8-15.

In the patent claim 22, Waugh et al. (A) teach that the positively charged backbone molecule has formula: $(gly)_{n1}(arg)_{n2}$ HIV-Tat or fragment thereof, wherein n1 = 2 to 5, and n2 =7 to 17, as applied to instant claims 22-27, and 197-203.

On pages 14-15, Waugh et al. (A) teach that the positively charged backbone molecule is a HIV-Tat fragment comprising amino acid sequence $(gly)_p$-RGRDDRRQRRR-$(gly)_q$ or $(gly)_p$-YGRKKRRQRRR-$(gly)_q$, wherein p and q are each independently an integer of from 0 to 20, as applied to instant claims 28-29, 204 and 206.

Waugh et al. (A) amino acid sequence of YGRKKRRQRRR *comprises* polylysine (KK) and polyarginine (RRR), as applied to instant claims 207-208.

Waugh et al. (A) teach that the positively charged backbone molecule can be a peptoid, i.e., a non-polypeptide molecule (see page 13, the 3rd paragraph), as applied to instant claims 16 and 209.

Waugh et al. (A) teach a process of administering the composition comprising the therapeutically active VEGF and said positively charged backbone molecule to a subject via transdermal delivery (a topical administration) (see page 36, lines 10-14), as applied to instant claims 78-80.

In the patent claims 6-9 and 13, Robbins et al. teach a peptide-cargo complex comprising the positively charge polypeptide, e.g., SEQ ID

**Supplemental Box**
**In case the space in any of the preceding boxes is not sufficient.**

NOs:97-99 (claim 6) and the cargo molecule which is therapeutic protein (claim 9), e.g., capspase-3 and HIV thymidine kinase and p53 (claim 13), as applied to instant claims 1-3.

In Tables 6-7 and Example 4 ([0183]), Robbins et al. teach a positively charged polypeptide which is TAT-PTD of amino acid sequence YGRKKRRQRRR (SEQ ID NO:21), i.e., HIV-Tat, and antennapedia PTD peptide of amino acid sequence RQIKIWFQNRRMKWKK (SEQ ID NO: 19), as applied to instant claims 197 and 204-208.

The above Robbins' polypeptides read on the instant peptide formula: $(gly)_{n1}(arg)_{n2}$, wherein n1 = 0 to 20, and n2 = 5 to 25, set forth in claim 198. The Robbins' teaching thus is applied to instant claims 198-203.

Robbins et al.. teach a kit comprising said the peptide-cargo complex, as applied to instant claims 72 and 74-75.

Also, Robbins et al. teach administering a composition (a peptide-cargo) comprising the positively charged polypeptide (the patent claims 25-29) and the cargo molecule which is biologically active protein and has therapeutic use, e.g., p53 and caspase-3; wherein the said administration is delivered to lung epithelial cells (i.e., topical delivery) (claim 30). The Robbins' teachings are applied to instant claims 78-80.

Hunt teaches a composition comprising polylysine and botulinum toxin (BT) which a biologically active protein, and association between the polylysine and BT is non-covalent (see [0190]), as applied to instant claims 1-3, 8 and 68.

Because BT protein (a heterodimer) has approximately 150 KD molecular weight molecular weight ( ≅150 KD), the Hunt's teaching is applied to instant claims 7-9.

Hunt teaches botulinum toxin type B, C.sub.1, D, E, F, or G (see [0199] and the patent claim 12), as applied to instant claim 69.

Hunt teaches that the BT is modified (see [0110]) and recombinantly produced (see [0142]), as applied to instant claims 70-71.

Since the kit set forth in instant claim 72 is considered to be a composition which comprises the same component, i.e., the passively charged backbone molecule (the polylysine thereof), the above Hunt's teachings are applied to instant claims 72-73.

In the patent claim 65, Dowdy teaches a positively charged polypeptide comprising AGKKRRQRRR (SEQ ID NO:2) which reads on the amino acid sequence of $(gly)_p$-YGRKKRRQRRR-$(gly)_q$ set forth in instant claims 204 and 206.

The above Dowdy's polypeptides further comprise peptide, i.e., polylysine (KK) and/or polyarginine (RRR), as applied to instant claims 207-208.

In the patent claims 1 and 99, Dowdy teaches a protein transduction composition comprising antennapedia homeodomain, as applied to instant claim 205.

In the patent claims 1-4, Park et al. disclose a copolymer comprising polyarginine or polylysine and poly[α-(4-aminbutyl)-L-glycolic acid] (PAGA) which comprises positively charged amine groups (see Figure 1) and is non-peptide polymer, as applied to instant claims 197 and 209. Note that claim 197 as written is directed to a positively-charged backbone polymer comprising polyarginine because when n1 is zero, the peptide formula of claim 197 reads on a poly(arg), i.e., $(arg)_{n2}$ wherein n2 = 5 to 25.

Chen et al. teach a copolymer composition comprising polyethyleneimine and polyarginine (see [0094]). Since claim 197 as written is directed to a positively-charged backbone polymer comprising polyarginine (see when n1 is zero, the peptide formula of claim 197 reads on a poly(arg), i.e., $(arg)_{n2}$ wherein n2 = 5 to 25), the Chen et al. teaching is applied to instant claims 197, 206-207 and 209-211.

In the patent claims Qin et al. teach a composition comprising copolymer having polyethyleneimine and polyarginine, as applied to instant claims 197, 206-207 and 209-211 (for the reason, see the above statement).

Schwartz et al. teach a composition for protein delivery (see abstract); the said composition comprising a therapeutic protein and a carrier molecule, e.g., HIV-tat sequence YGRKKRRQRRR, polypeptide having polylysine subsequences and antennapedia peptide, all which are positively-charged (see Table 2), as applied to instant claims 1-11 and 22-23, 28-33, 197-198 and 203-208.

On pages 9-10, Waugh et al. teach that the composition for delivery therapeutic agent e.g., biologically active protein, comprises poly-lysine, wherein the poly-lysine have MW □ 70 KD, or between 150 and 300 KD, as applied to instant claims 9-15.

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**Supplemental Box**
**In case the space in any of the preceding boxes is not sufficient.**

Waugh et al. teach that the positively charged backbone molecule can be a peptoid, i.e., a non-polypeptide molecule (see page 8, the 2nd paragraph), as applied to instant claims 16 and 209.

The sequence YGRKKRRQRRR comprises at least three consecutive arginine residues, as applied to instant claims 24-25 and 199-200.

In the patent claims 1-3, Waugh et al. (B) teach a composition comprising a biologically active agent (e.g., botulinum toxin (BT), se claim 3), and a polymer having a positively charged backbone, as applied to instant claims 1-3 and 68-71.

In the patent claim 39, Waugh et al. (B) teach a kit comprising the above-mentioned composition, as applied to instant claims 73-75.

In the patent claims 28 and 33, Waugh et al. (B) teach a transdermal (topical administering) delivering the said composition comprising therapeutic agent (protein), as applied to instant claims 78-80.

Because BT protein (a heterodimer) has approximately 150 KD molecular weight molecular weight ( abour 150 KD), the Waugh et al. teaching is applied to instant claims 7-8.

In the patent claims 11-12, Waugh et al. (B) teach the said polymer is HIV-TAT polypeptide or fragment thereof, or polypeptide comprising $(gly)_n$-RRRRRRR (n= 0 to 20), as applied to instant claim 22-28 and 31-32.

In the patent claims 15-17, Waugh et al. (B) teach that the said HIV-TAT polypeptide has sequence: $(gly)_p$-YGRKKRRQRRR-$(gly)_q$, wherein p and q are each independently an integer of from 0 to 20, as applied to instant claims 29.

The above sequence comprises polylysine (KK), as applied to instant claim 33.

In the patent claims 12-14, Waugh et al. (B) teach that HIV-TAT or fragment thereof, and a polypeptide comprising $(gly)_n$-RRRRRRR (n= 0 to 20), as applied to instant claim 22-29, 197-204 and 206-207.

Mahato et al. teach composition for delivery bioactive protein comprising positively charged polyethyleneimine (PEI) and the protein to be locally deliver, i.e., tropical administration (see Example 13 and abstract), wherein PEI is non-peptide compound, as applied to instant claims 1 and 16 -18.

Mahato et al. teach that the average molecular eight of PEI is about 25,000 Daltons (see column 3, lines 30-35, and column 9, line 32), as applied to instant claim 19.

Apt et al. teach a composition comprising protein complexed with positively charged poly(ethylenimine) or polylysine (see ([0422]), wherein the protein for transdermal protein administration is further formulated with transdermal patch devices, i.e., skin patch (see [0424]), as applied to instant claims 1, 72 and 74-75.

Claims 1, 16 and 17-21 lack inventive step under PCT Article 33(3) as being obvious over Mahato R. I. et al. (US Pat. No. 6696038) taken with Swann (US Pat. No. 4434228).

Mahato et al. teach composition for delivery bioactive protein comprising positively charged polyethyleneimine (PEI) and the protein to be locally deliver, i.e., tropical administration (see Example 13 and abstract), wherein PEI is non-peptide compound, as applied to instant claims 1 and 16 -18. Also, Mahato et al. teach that the average molecular eight of PEI is about 25,000 Daltons (see column 3, lines 30-35, and column 9, line 32), as applied to instant claim 19.

Yet, Mahato et al. do not expressly teach PEI molecular weight is between 25 KD and 1000 KD.

Swann teaches high molecular weight PEI having MW: 30 KD to 100 KD (see column 2, lines 49-55), which is water soluble (see column 2, lines 64-65); when formulated with biomolecule, there is little influence on biological activity of the biomolecule (see columns 1-2), as applied to instant claims 20-21.

It would have been obvious to one skilled in the art at the time the invention was made to formulate the PEI with bioactive molecule, e.g., bioactive protein so as to deliver the protein to a target site. One skilled in the art would have done this because the synthesized PEI is only water soluble but also durable for biopolymer which associated with the PEI polymer without adverse effect on the biopolymer activity (see column 2, lines 27-32 and 41-43).

Claims 1-3, 7-33, 68-75, 78-80 and 197-211 meet the requirement of PTC article 33(4), because the claimed compositions and method are useful in delivery of therapeutically active polypeptide or protein.

# CHAPTER I
# PCT TELEPHONE MEMORANDUM
# FOR
# LACK OF UNITY OF INVENTION

PCT No.: PCT/US05/06930

Examiner: Samuel W. Liu

Attorney spoken to: Joseph Eng, Jr.

Date of call: 03 August 2005

☒ Amount of payment approved: $1,000.00

☒ Deposit account number to be charged: 134-500

☐ Attorney elected to pay for ALL additional inventions

☒ Attorney elected to pay only for the additional inventions covered by

☒ Group(s): 4

-- encompassing –

☒ Claim(s): claims 78-80

☐ Attorney elected NOT to pay for any additional inventions, therefore, only the first claimed invention (Group I) covered by Claim(s) _____ has been searched.

☒ Attorney was orally advised that there is no right to protest for any group not paid for.

☒ Attorney was orally advised that any protest must be filed no later than 15 days from the mailing of the Search Report (PCT/ISA/210).

**Time Limit For Filing A Protest**

Applicant is hereby given 15 days from the mailing date of this Search Report in which to file a protest of the holding of lack of unity of invention. In accordance with PCT Rule 40.2, applicant may protest the holding of lack of unity only with respect to the group(s) paid for.

**Detailed Reasons For Holding Lack of Unity of Invention:**

Please See Continuation Sheet

*Note: A copy of this form must be attached to the Search Report.*

# ATTACHMENT TO CHAPTER I PCT TELEPHONE MEMORANDUM FOR LACK OF UNITY OF INVENTION

**Continuation of Detailed Reasons For Holding Lack of Unity of Invention:**

Group 1, claims 1-3, 7-33, 68-75 and 197-211, drawn to a composition comprising a polypeptide and a carrier which has a positively charged backbone, and a kit comprising the composition thereof.

Group 2, claims 4-6, 34-67, 182-185 and 197-211, drawn to a composition comprising a non-polypeptide or/and non-polynucleotide agent and a carrier which has a positively charged backbone.

Group 3, claims 76-77 and 186-189, drawn to a kit comprising a device for delivering a biologically active protein to a subject and a composition comprising a positively charged carrier.

Group 4, claims 78-80, drawn to a method of administering a biologically active protein to a subject comprising delivering the protein and a positively charged carrier to the skin or epithelium of the said subject.

Group 5, claims 81-97 and 190-196, drawn to a method of administering a non-protein non-nucleic acid molecule to a subject comprising delivering the molecule and a positively charged carrier to the skin or epithelium of the said subject.

Group 6, claims 98-140, drawn to a composition comprising an antigen for immunization and a carrier which has a positively charged backbone.

Group 7, claims 141-181 and 184, drawn to a method of administering the antigen for immunization and a positively charged carrier to the skin or epithelium of the said subject.

Group 8, claim 212, drawn to a composition comprising a non-covalent complex comprising (i) a positively charged backbone, and (ii) at least tow of members: (a) a negatively charged backbone having a plurality of attached imaging moieties, (b) a negatively charged backbone having a plurality of attached targeting moieties, (c) polynucleotide, and/or (d) a negatively charged backbone having a plurality of attached biological agent.

Group 9, claim 213, drawn to a method of preparing a composition comprising a positively charged backbone and at least tow of members: (a) a negatively charged backbone having a plurality of attached imaging moieties, (b) a negatively charged backbone having a plurality of attached targeting moieties, (c) polynucleotide, and/or (d) a negatively charged backbone having a plurality of attached biological agent.

Group 10, claims 214-218, drawn to a composition comprising insulin and a carrier having positively charged backbone, and a kit comprising said composition.

Group 11, claims 219-220, drawn to a method of administering the insulin to a subject comprising delivering to the subject the insulin and a positively charged carrier.

Group 12, claims 221-228, drawn to a composition comprising imaging agent and a targeting agent and a positively charged backbone, and a kit comprising said composition.

Group 13, claims 229-238, drawn to a method of administering the composition of Group 12 to a subject comprising delivering to the skin or epithelium of subject the said composition.

*Note: A copy of this form must be attached to the Search Report.*

Group 14, claim 239, drawn to a composition comprising a positively charged backbone and at least tow of members: (a) a negatively charged backbone having a plurality of attached imaging moieties, (b) a negatively charged backbone having a plurality of attached targeting moieties, (c) a negatively charged backbone having a plurality of attached biological agent.

Group 15, claim 240, drawn to a method of preparing the composition of Group 14 to a subject comprising combining a positively charged backbone component and at least tow of members: (a) a negatively charged backbone having a plurality of attached imaging moieties, (b) a negatively charged backbone having a plurality of attached targeting moieties, (c) a negatively charged backbone having a plurality of attached biological agent.

The inventions listed as Groups 1-15 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The special technical feature of Group 1 is directed to a composition comprising bioactive polypeptide and a carrier which has a positively charged backbone, which is not a contribution over the prior art as Waugh et al. (WO 03072049) patent application teaches a composition comprising a biologically active polypeptide, i.e., vascular endothelial growth factor (VEGF), and a carrier molecule which structure reads on the peptide formula set forth in instant claim 29; the said carrier molecule comprises a positively charged backbone having a plurality of attached efficiency groups (see the patent claim 19) wherein association between the VEGF and the carrier molecule is non-covalent. The Waugh et al. teachings are applied to instant claims 1-3 and 22. Thus, the invention lacks unity of invention.

*Note: A copy of this form must be attached to the Search Report.*